Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 10287–10294

TETRAHEDRON

Synthesis of the tricyclic dihydrofuran moiety of azadirachtin: efficient transformation of the Claisen rearrangement intermediate into a functionalized tricyclic dihydrofuran core

Jun Ishihara,[a,*] Yohei Ikuma,[b] Susumi Hatakeyama,[a] Takanori Suzuki[b] and Akio Murai[b]

[a]*Graduate School of Biomedical Sciences, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki 852-8521, Japan*
[b]*Division of Chemistry, Graduate School of Science, Hokkaido University, Sapporo 060-0810, Japan*

Received 28 August 2003; accepted 14 October 2003

Abstract—Azadirachtin is a *C-seco* limonoid, derived from the neem tree. Previously, we reported the synthesis of the right and left segments of azadirachtin, in addition to the coupling reaction of the modeled ester utilizing Claisen rearrangement. Herein we report the transformation of the modeled rearrangement product into a tricyclic dihydrofuran, which would be expected to have bioactivity against insects.

1. Introduction

The higher plants have acquired chemical defence mechanisms against the attack of pathogens and insects. Tropical trees, especially, are known to have the highly elaborated chemical defence mechanisms, which have gradually been elucidated by recent progress of biochemistry.[1] Azadirachtin (**1**) is a *C-seco* limonoid, isolated in 1968 from the seeds of Indian neem tree, *Azadirachta indica* A. Juss (Fig. 1).[2] This natural product has shown strong bioactivity against insects, including repellent and antifeedant activities. Despite its high insect antifeedant activity, azadirachtin shows no apparent phytotoxicity and is remarkably non-toxic to higher animals. The structure and relative stereochemistry were clarified in 1985 by Kraus and Ley,[3] and the absolute configuration was determined in 1992.[4] Although several groups have reported synthetic studies on azadirachtin,[5] total synthesis has not yet been achieved. The biological studies[6] and structure–activity relationships[7] of **1** have been investigated utilizing various derivatives. Ley and co-workers demonstrated that the stereochemistry at C-7 and the bridging oxygen substituent at C-6 are responsible for insect antifeedant activity using various derivatives and degradative compounds.[8] Interestingly, they also showed that the tricyclic dihydrofuran moiety, the right wing moiety, had still rather potent antifeedant activity.[9] Recently, conformational calculations have been carried out by Baldoni and co-workers in order to determine the structural characteristics responsible for the biological activity.[10] In the course of our synthetic studies on **1**, we found that the coupling between the left and right moieties could be cleanly achieved by means of Claisen rearrangement of the corresponding ester.[11] We were therefore interested in the transformation of the modeled rearrangement product into the functionalized tricyclic

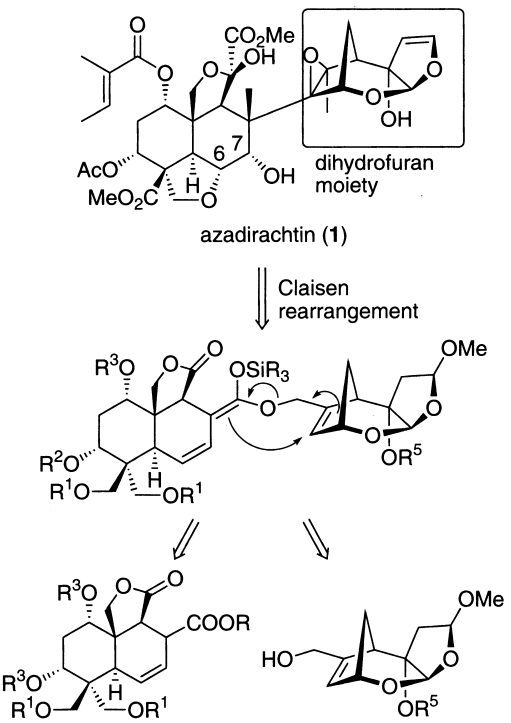


Figure 1.

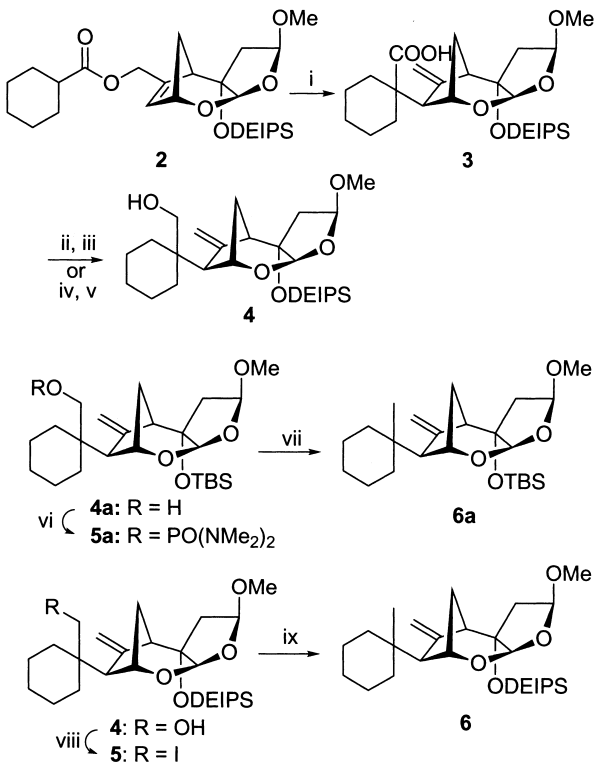
Keywords: azadirachtin; Claisen rearrangement; deoxygenation.
* Corresponding author. Tel./fax: +81-95-819-2427;
e-mail: jishi@net.nagasaki-u.ac.jp

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.10.062

dihydrofuran core of **1**, which would be expected to have bioactivity against insects.

2. Deoxygenation of hydroxyl group at neopentyl position

The Ireland–Claisen rearrangement of the modeled ester **2** readily proceeded to afford the carboxylic acid **3** in good yield as we previously reported (Scheme 1).[12] Methyl esterification of **3** and subsequent DIBAL-H reduction gave the alcohol **4**. Since lactone functionality must be installed into the genuine substrate, sequential conversion of **3** to **4** ($ClCO_2Et$, Et_3N, THF, 0°C and then $NaBH_4$, MeOH, −60°C)[13] would therefore be practically feasible. Compound **4a** could be also prepared by similar method to **4**.

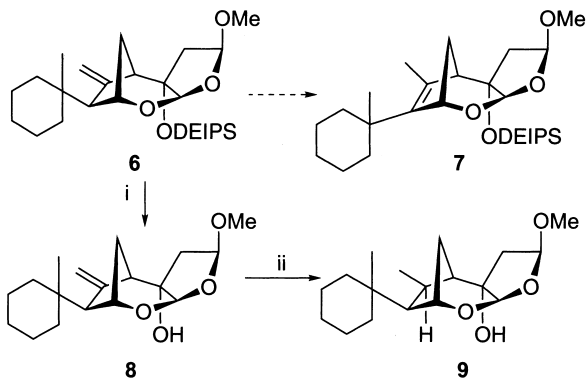


Scheme 1. Synthesis of methyl compound **6**. *Reagents and conditions*: (i) KHMDS, TMSCl/Et_3N, PhMe, −78→70°C, 12 h (87%); (ii) CH_2N_2, Et_2O, 0°C, 30 min; (iii) DIBAL-H, CH_2Cl_2, −78°C, 1 h (~100% for 2 steps); (iv) Et_3N, $ClCO_2Et$, THF, 0°C, 40 min; (v) $NaBH_4$, MeOH, −78→−60°C, 19 h (**4**: 60% for 2 steps, recovered **3**: 40%); (vi) LiHMDS, $(Me_2N)_2P(O)Cl$, THF, TMEDA, 23°C, 13 h (87%); (vii) Li naphthalenide, THF, 0→23°C (44%); (viii) imidazole, PPh_3, I_2, PhH, 23°C, 4 h (93%); (ix) $NaBH_4$, DMSO, 100°C, 2 h (87%).

Deoxygenation of the hydroxyl group in **4** and **4a** seemed to be difficult due to its hindered neopentyl position. We initially attempted a Barton–McCombie type process via xanthates under various conditions.[14] Disappointingly, treatment of the corresponding methyl dithiocarbonate, derived from **4a**, with AIBN/Ph_2SiH_2 or $(PhCOO)_2$/Ph_2SiH_2[15] furnished none of the desired products. In addition, Ph_2SiH_2-mediated radical reduction of the imidazoyl thiocarbonate also gave a complex mixture, presumably because the proximal *exo*-olefin reacted with the resulting primary radical. Alternatively, we tried alkaline metal reduction of phosphodiamidate (PON) in liquid ammonia, which is known to be amenable to the deoxygenation in complex molecules.[16] Hence, introduction of a PON group into **4a** readily afforded compound **5a**. We then subjected **5a** to Benkeser and Birch reductions, respectively. However, both reductions resulted in predominant hydrogenation of the *exo*-olefin rather than the deoxygenation. The desired deoxygenation was eventually achieved when **5a** was treated with lithium naphthalenide in THF,[17] resulting in **6a** in 44% yield. Meanwhile, exposure of **4** to $MeP(OPh)_3I$ and $NaBH_3CN$ in HMPA at 100°C[18] afforded **6** in 29% yield at single step. This result showed that hydride reduction of the iodide could proceed smoothly in this substrate. Consequently, we were pleased to find that iodination of **4** to **5** and subsequent $NaBH_4$ reduction in DMSO at 100°C generated **6** in 81% yield.[19]

3. Transformation of *exo*-olefin into *endo*-olefin

Next we envisaged isomerization of the *exo*-olefin in **6** to the *endo*-olefin **7** (Scheme 2). Although application of allyl isomerization using transition metals is well documented, compound **6** resisted those reactions.[20] All attempts of isomerization of **6** in the presence of transition metals [$RhCl(PPh_3)_3$/iPr_2NEt, $PdCl_2(PhCN)_2$, and $RhCl_3{\cdot}3H_2O$] were unsuccessful, most of which resulted in quantitative recovery of **6**. From these results it was postulated that the bulky DEIPS group inhibited the transition metal from approaching the allylic hydrogen to be reacted. These disappointing results led us to examine the allyl isomerization after removal of the DEIPS group. Crabtree catalyst $\{Ir(cod)[PCH_3(C_6H_5)_2]_2\}PF_6$,[21] a cationic catalyst, was considered an alternative because it would be accessible from the α-side in **8** via its coordination to the hydroxyl group. Unfortunately, treatment of **8** with Crabtree catalyst furnished the saturated compound **9** in 40% yield, along with recovery of **8** in 60% yield. According to the stereochemistry at hydrogenated position in **9**, the catalyst apparently was able to coordinate to the hydroxyl group at α-side however was unable to cause the isomerization.



Scheme 2. Attempted reactions for allyl isomerization. *Reagents and conditions*: (i) Bu_4NF, THF, 0°C, 40 min (100%); (ii) $\{Ir(cod)[PCH_3(C_6H_5)_2]_2\}PF_6$, THF, 40°C (40%, **8**: 60%).

Recently, Ley demonstrated that the primary radical **10a** was predominantly captured by hydrogen radical over the tertiary radical **10b** owing to the steric hindrance (Fig. 2).[5k] This result prompted us to attempt the isomerization by radical reaction. Breslow and Baldwin have developed the

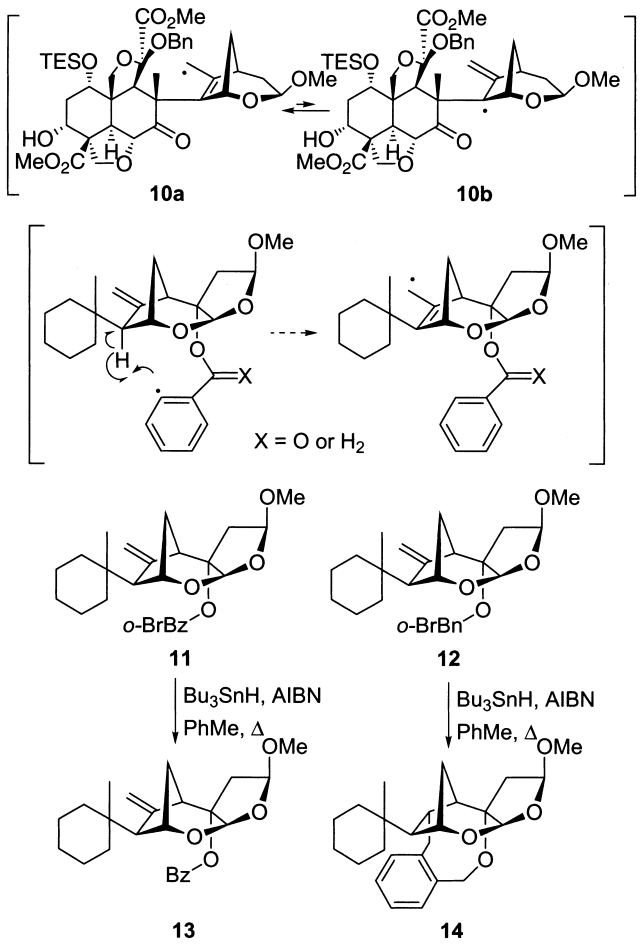


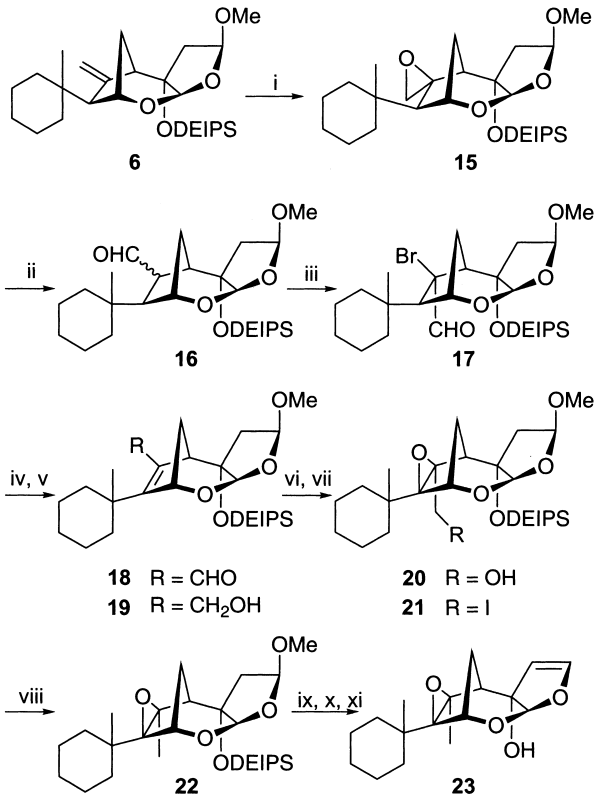
Figure 2.

ingenious remote oxidations, which were controlled by remote functionalities excited by photo-irradiation.[22] It was therefore hoped that the α-bromobenzoate group in **11** or the α-bromobenzyl group in **12** could serve as a remote functionality to induce the allyl radical preferentially. Unfortunately, these methodologies concluded unsatisfactorily to give compounds **13** and **14**, respectively.

All other attempts of allylic isomerization ($PhSO_2NSO$,[23] NBS/$h\nu$ NIS/iPr$_2$NEt or SeO_2) for **6** were unsuccessful.

In this event, we found an alternative route for the transformation of the *exo*-olefin to the *endo*-olefin (Scheme 3). This route commenced with the epoxidation of **6** with *m*CPBA affording **15** exclusively in 90% yield,[24] followed by treatment with $BF_3{\cdot}OEt_2$ at −55°C to give a mixture of aldehydes **16** (3.1:1) in 78% yield. When we performed the bromination at α-position of the aldehyde with KHMDS, HMPA and NBS in THF at −60°C, the bromide **17** was obtained in 71% yield. Fortunately, the elimination of the bromide with LiBr and Li_2CO_3 in DMF proceeded smoothly to generate the α,β-unsaturated aldehyde **18** in 97% yield.[25]

Having established a procedure for the transformation of *exo*-olefin into *endo*-olefin, we turned our attention towards the final part of the synthesis. Luche reduction[26] of **19** with $NaBH_4$, $CeCl_3{\cdot}7H_2O$ in MeOH, followed by epoxidation



Scheme 3. Synthesis of *endo*-olefin compound. *Reagents and conditions*: (i) *m*CPBA, $NaHCO_3$, CH_2Cl_2, 23°C, 18 h (90%); (ii) $BF_3{\cdot}Et_2O$, CH_2Cl_2, −55°C, 7 h (78%) (α:β=3;1); (iii) KHMDS, HMPA, THF, −55°C, 20 min then NBS, 2 h (71%); (iv) LiBr, Li_2CO_3, DMF, 125°C, 13 h (97%); (v) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0°C, 1 h (78%); (vi) $VO(acac)_2$, TBHP, CH_2Cl_2, 23°C, 3.5 h (100%); (vii) I_2, PPh_3, Imidazole, THF 23°C, 8 h (82%); (viii) $NaBH_4$, MeCN, reflux, 18 h (88%); (ix) PhSeH, Amberlyst-15, MS-4A, CH_3CN, 25°C, 30 min; (x) H_2O_2, Py, CH_2Cl_2, 0°C, 30 min (recovered **22**: 22%); (xi) Bu_4NF, THF, 0°C, 10 min (19% for 3 steps).

with $VO(acac)_2$, TBHP afforded the epoxide **20** exclusively in a good yield. The stereochemistry of the epoxide could be confirmed by NOESY spectra of **20**. It was postulated that the reagent was accessible to the less hindered β-side of the tricyclic molecule, thus generating the desired selectivity. The second deoxygenation was performed under the similar conditions to those described for **5**. Treatment of **20** with I_2, Ph_3P and imidazole furnished iodide **21** which after subsequent $NaBH_4$ reduction in CH_3CN successfully afforded **22** in 88% yield. It should be noted that the epoxide was intact under the reduction conditions. The transformation of **22** into dihydrofuran was accomplished by Ley's procedure.[27] Selenylation of **22** and oxidation formed the dihydrofuran, which was followed by removal of DEIPS with Bu_4NF to give the desired tricyclic dihydrofuran **23** in 19% yield for 3 steps, accompanied by recovery of **22** in 22% yield.

4. Conclusion

The Claisen rearrangement product **3** was converted into the deoxygenated compound **6** via sequential iodination and $NaBH_4$ reduction in good yield. Although direct isomerization of the *exo*-olefin of **6** to the *endo*-olefin was fruitless, an alternative route involving transformation of **6** into the α,β-aldehyde **18** could be established. The aldehyde **18** was

converted into the desired tricyclic dihydrofuran **23** via selective epoxidation and deoxygenation. Consequently, we have developed an efficient method for the transformation of the rearranged product into the tricyclic dihydrofuran. The biological activity of **23** thus prepared is under investigation.

5. Experimental

5.1. General information

Solvents and reagents were dried and distilled before use. Tetrahydrofuran (THF) and toluene (PhMe) were distilled from sodium benzophenone ketyl. CH_2Cl_2, pyridine, and Et_3N were distilled from CaH_2. DMSO was distilled under reduced pressure from CaH_2. EtOH and MeOH were distilled from their magnesium alkoxides. Normal reagent-grade solvents were used for flash chromatography and extraction. All reactions were monitored by TLC with precoated Silica gel plates (Merck, silica gel 60 F_{254} 1.05715.25). Visualization was achieved via UV light, a 5.6% ethanolic *p*-anisaldehyde solution containing 5.6% of concentrated H_2SO_4-heat, and 10% ethanolic phosphomolybdic acid solution-heat. For flash chromatography was utilized Silica gel (YMG, silica gel SIL-60-400/230W or Kanto Kagaku, silica gel 60N, spherical neutral, 37563-84). Melting points were measured in open capillary tubes and are uncorrected. IR spectra were obtained on a Hitachi model 270-30 and JASCO model FT/IR-230 infrared spectrophotometer in neat state. The ^1H NMR spectra were recorded on a JEOL model AL-300 (300 MHz), α-400 (400 MHz) and a VARIAN model Gemini 300 (300 MHz) spectrometers in $CDCl_3$. The ^{13}C NMR spectra were measured on a VARIAN Gemini 300 (75 MHz), Unity plus 500 (125 MHz) and spectrometer in $CDCl_3$. Chemical shifts (δ) were reported with tetramethylsilane (δ=0.00 ppm) or $CHCl_3$ (δ=7.26 ppm) as internal standards. Splitting patterns were designated as 's, d, t, q, m, and br'; indicating 'singlet, doublet, triplet, quartet, multiplet, and broad,' respectively. Optical rotations were recorded on JASCO model DIP-370 and P-1020 digital polarimeters using $CHCl_3$ as a solvent. High-resolution mass spectra were obtained on a JEOL model JMS-HX-110 and JMS-DX303 mass spectrometer under EI condition. All reactions were carried out under anhydrous conditions and argon atmosphere, unless otherwise noted.

5.1.1. Cyclohexanecarboxylic acid (1*R*,2*S*,4*S*,6*R*,8*S*)-2-(diethylisopropylsilyloxy)-4-methoxy-5,7-dioxatricyclo[6.2.1.0^{2,6}]undec-9-en-10-ylmethyl ester (2). To a mixture of EDCI·HCl (1.66 g, 8.66 mmol) and DMAP (1.02 g, 7.31 mmol) in CH_2Cl_2 (10 mL) was added cyclohexanecarboxylic acid (937 mg, 7.31 mmol) at 0°C. After stirring for 15 min, a solution of allyl alcohol (1.19 g, 3.34 mmol) in CH_2Cl_2 (10 mL) was added dropwise and stirring was continued at 23°C for 2 h. The mixture was diluted with sat. NH_4Cl (30 mL), and the aqueous layer was extracted with Et_2O (3×30 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was subjected to flash chromatography (silica gel 50 g, hexane:EtOAc, 10:1 to 6:1) to afford **2** (1.43 g, 3.06 mmol, 92%) as a colorless oil; $[\alpha]_D^{26}$=+70.2 (*c* 2.27, $CHCl_3$); ν_{max} (cm^{-1}) (neat) 2935, 2863, 1737, 1452, 1365, 1315, 1274, 1247, 1195, 1166, 1132, 1101, 1074, 1029, 962, 937, 881, 844, 761, 727, 665; δ_H (300 MHz, $CDCl_3$) 5.95 (1H, brd, *J*=2.4 Hz), 5.31 (1H, dd, *J*=3.9, 5.9 Hz), 4.92 (1H, s), 4.86 (1H, d, *J*=1.7 Hz), 4.80 (1H, d, *J*=1.9 Hz), 4.63 (1H, br s), 3.44 (3H, s), 2.90 (1H, brd, *J*=5.0 Hz), 2.39–2.29 (1H, m), 2.35 (1H, dd, *J*=5.9, 15.2 Hz), 2.29 (1H, dd, *J*=3.9, 15.2 Hz), 2.12 (1H, brd, *J*=11.6 Hz), 1.92–1.85 (1H, m), 2.05–1.24 (10H, m), 1.00–0.89 (13H, m), 0.70–0.61 (4H, m); EI-MS-LR *m*/*z* (Int.%), 466 (M^+, 7), 437 (M^+-Et, 3), 423 (M^+-iPr, 12), 389 (64), 338 (68), 293 (49); EI-MS-HR, calcd for $C_{22}H_{35}O_6Si$ (M^+-iPr): 423.2203, found 423.2200.

5.1.2. (1*R*,2*S*,4*S*,6*R*,8*S*)-1-{2-(Diethylisopropylsilyloxy)-4-methoxy-10-methylene-5,7-dioxatricyclo[6.2.1.0^{2,6}]-undec-9-yl}-cyclohexanecarboxylic acid (3). To a solution of **2** (367 mg, 0.79 mmol) in PhMe (7 mL) was added a solution of KHMDS (0.5 M in PhMe, 6.3 mL, 3.15 mmol) at −78°C and the mixture was stirred at −78°C for 1 h. A mixture of TMSCl (2.5 mL, 19.7 mmol) and Et_3N (2.5 mL, 17.9 mmol) in PhMe (2.5 mL) was centrifuged at 2000 rpm for 5 min and the supernatant (3.0 mL) was added to the reaction mixture at −78°C. The stirring mixture was warmed gradually to 70°C over 3 h and stirring was continued at the same temperature for an additional 11 h. The solution was cooled to the ambient temperature, and the reaction was diluted with sat. NH_4Cl (10 mL) at 0°C. The mixture was adjusted to pH 3 by 2 M HCl, and the aqueous layer was extracted with Et_2O (2×15 mL). Drying over $MgSO_4$, concentration, and flash chromatography (silica gel 13 g, hexane:EtOAc, 6:1) afforded **3** (264 mg, 0.57 mmol, 72%) as a white amorphous; $[\alpha]_D^{26}$=+22.5 (*c* 1.01, $CHCl_3$); ν_{max} (cm^{-1}) (neat) 3095, 2937, 2875, 1727, 1699, 1461, 1454, 1413, 1380, 1322, 1284, 1270, 1240, 1191, 1170, 1132, 1081, 1037, 1012, 966, 937, 898, 881, 761, 725, 665; δ_H (300 MHz, $CDCl_3$) 5.30 (1H, dd, *J*=4.0, 6.2 Hz), 5.26 (1H, br s), 5.18 (1H, br s), 4.91 (1H, s), 4.48 (1H, br s), 3.43 (3H, s), 2.87 (1H, br s), 2.77 (1H, brd, *J*=5.0 Hz), 2.33 (1H, dd, *J*=4.0, 15.0 Hz), 2.25 (1H, dd, *J*=6.2, 15.0 Hz), 2.14 (1H, brd, *J*=10.6 Hz), 2.05–2.02 (2H, m), 1.62 (4H, m), 1.48–1.15 (5H, m), 1.00–0.89 (13H, m), 0.68–0.60 (4H, m); EI-MS-LR *m*/*z* (Int.%), 437 (M^+-Et, 9), 423 (M^+-iPr, 100), 391 (36), 293 (76); EI-MS-HR, calcd for $C_{22}H_{35}O_6Si$ (M^+-iPr): 423.2203, found: 423.2205.

5.1.3. {1-[(1*R*,2*S*,4*S*,6*R*,8*S*)-2-Diethylisopropylsilyloxy-4-methoxy-10-methylene-5,7-dioxatricyclo[6.2.1.0^{2,6}]-undec-9-yl]-cyclohexyl}-methanol (4). To a solution of **3** (13.8 mg, 29.6 μmol) in THF (0.5 mL) were added Et_3N (8.3 μL, 59.6 μmol) and ethyl chloroformate (5.7 μL, 59.6 μmol) at 0°C, and the mixture was stirred at 0°C for 40 min. The mixture was diluted with MeOH (0.2 mL), and $NaBH_4$ (7.8 mg, 206 μmol) was then added to the reaction mixture at −78°C. The solution was stirred at −78°C for 20 h, at −70°C for 46.5 h, and then at −60°C for 19 h. To the mixture was added 0.5 M HCl (2 mL), and the aqueous layer was extracted with Et_2O (3×3 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was subjected to flash chromatography (silica gel, 3 g, hexane:EtOAc, 5:1) to afford **4** (8.1 mg, 17.8 μmol, 60%) as a pale yellow oil, along with carboxylic acid **3** (5.5 mg, 11.8 μmol, 40%). **4**;

$[\alpha]_D^{26}$=+37.5 (*c* 0.91, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 5.30 (1H, dd, *J*=4.0, 6.2 Hz), 5.29 (1H, br s), 5.25 (1H, br s), 4.91 (1H, s), 4.50 (1H, br s), 3.56–3.48 (2H, m), 3.44 (3H, s), 2.79 (2H, m), 2.36 (1H, dd, *J*=4.0, 15.0 Hz), 2.25 (1H, dd, *J*=6.2, 15.0 Hz), 2.05 (1H, brd, *J*=12.8 Hz), 1.78 (1H, ddd, *J*=2.8, 5.9, 12.8 Hz), 1.70–1.45 (10H, m), 1.01–0.88 (13H, m), 0.69–0.60 (4H, m); ν_{max} (cm^{-1}) (neat) 3477, 2931, 2865, 1461, 1415, 1380, 1348, 1322, 1299, 1270, 1238, 1189, 1133, 1072, 1037, 966, 941, 900, 881, 858, 757, 725, 665, 559 cm^{-1}; EI-MS-LR *m/z* (Int.%), 437 (65), 409 (M^+-iPr, 34), 377 (30), 293 (100); EI-MS-HR, calcd for $C_{22}H_{37}O_5Si$ (M^+-iPr): 409.2410, found: 409.2400.

5.1.4. 1-{(1*R*,2*S*,4*S*,6*R*,8*S*)-2-Diethylisopropylsilyloxy-4-methoxy-10-methylene-5,7-dioxatricyclo[6.2.1.0^{2,6}]-undec-9-yl}-1-iodomethyl-cyclohexane (5). To a solution of alcohol **4** (989 mg, 2.06 mmol) in PhH (10 mL) were added imidazole (750 mg, 11.0 mmol), PPh_3 (2.74 g, 10.4 mmol), and a solution of I_2 (2.60 g, 10.2 mmol) in PhH (8 mL). After stirring at 23°C for 11 h, the reaction was diluted with ether and sat. $NaHCO_3$ (5 mL). To the mixture was added a solution of I_2 in PhH until the solution persisted in yellow–brown color. After addition of sat. $Na_2S_2O_3$ (20 mL), the mixture was extracted with ether (3×25 mL), dried over $MgSO_4$, and concentrated. The residue was subjected to flash chromatography (silica gel, 30 g, hexane:EtOAc, 8:1) to furnish iodide **5** (1.08 g, 1.92 mmol, 93%) as a pale yellow amorphous; $[\alpha]_D^{26}$=+64.4 (*c* 0.67, $CHCl_3$); ν_{max} (cm^{-1}) (neat) 2931, 2865, 1460, 1376, 1237, 1190, 1167, 1132, 1105, 1080, 1069, 1037, 966, 937, 881, 758, 722, 665, 603; δ_H (300 MHz, $CDCl_3$), 5.30 (1H, dd, *J*=4.2, 6.1 Hz), 5.29 (1H, br s), 5.25 (1H, br s), 4.94 (1H, s), 4.44 (1H, br s), 3.52 (1H, d, *J*=10.5 Hz), 3.44 (3H, s), 3.42 (1H, d, *J*=10.5 Hz), 2.85 (1H, br s), 2.76 (1H, brd, *J*=5.5 Hz), 2.34 (1H, dd, *J*=4.2, 14.9 Hz), 2.24 (1H, dd, *J*=6.1, 14.9 Hz), 2.04 (1H, brd, *J*=12.8 Hz), 1.68–1.17 (11H, m), 1.01–0.85 (13H, m), 0.69–0.61 (4H, m); EI-MS-LR *m/z* (Int.%) 533 (M^+−Et, 3), 519 (M^+-iPr, 70), 487 (27), 437 (31), 293 (100); EI-MS-HR, calcd for $C_{22}H_{36}O_4ISi$ (M^+-iPr): 519.1428; found: 519.1425.

5.1.5. 1-{(1*R*,2*S*,4*S*,6*R*,8*S*)-2-Diethylisopropylsilyloxy-4-methoxy-10-methylene-5,7-dioxatricyclo[6.2.1.0^{2,6}]-undec-9-yl}-1-methylcyclohexane (6). To a solution of **5** (4.8 mg, 8.5 μmol) in DMSO (0.5 mL) was added $NaBH_4$ (ca. 10 mg, excess) at 23°C, and the mixture was stirred at 100°C for 2 h. The mixture was diluted with 0.5 M HCl (2.0 mL), and the aqueous layer was extracted with Et_2O (3×3 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was subjected to flash chromatography (silica gel, 0.8 g, hexane:EtOAc, 15:1) to afford **6** (3.2 mg, 7.4 μmol, 87%) as a colorless oil; $[\alpha]_D^{25}$=+38.6 (*c* 0.35, $CHCl_3$); ν_{max} (cm^{-1}) (neat) 2929, 2864, 1462, 1414, 1376, 1322, 1299, 1284, 1270, 1239, 1189, 1168, 1132, 1105, 1077, 1037, 1015, 966, 940, 912, 882, 858, 761, 731, 665, 647, 576; δ_H (300 MHz, $CDCl_3$) 5.30 (1H, dd, *J*=4.0, 6.2 Hz), 5.23 (1H, br s), 5.18 (1H, br s), 4.91 (1H, s), 4.43 (1H, br s), 3.44 (3H, s), 2.74 (1H, d, *J*=5.7 Hz), 2.62 (1H, br s), 2.35 (1H, dd, *J*=4.0, 14.9 Hz), 2.24 (1H, dd, *J*=6.2, 14.9 Hz), 2.00 (1H, brd, *J*=12.7 Hz), 1.64 (1H, ddd, *J*=2.7, 5.7, 12.7 Hz), 1.55–1.25 (10H, m), 1.00–0.92 (13H, m), 0.81 (3H, s), 0.69–0.60 (4H, m); EI-MS-LR *m/z* (Int.%) 436 (M^+, 0.7), 393 (M^+-iPr, 88), 361 (38), 293 (100), 265 (47); EI-MS-HR, calcd for $C_{25}H_{44}O_4Si$ (M^+): 436.3009, found: 436.3008.

5.1.6. 1-{(1*R*,2*S*,4*S*,6*R*,8*S*,10*R*)-2-Diethylisopropylsilyl-oxy-4-methoxy-10-methylene-5,7-dioxa-10-oxirane-spiro-tricyclo[6.2.1.0^{2,6}]undec-9-yl}-1-methylcyclo-hexane (15). To a stirred mixture of **6** (8.9 mg, 20.4 μmol) in CH_2Cl_2 (1 mL) were added *m*CPBA (10.5 mg, 0.0608 mmol) and $NaHCO_3$ (12.0 mg, 0.143 mmol) at 0°C, and the mixture was stirred at 23°C for 18 h. The reaction mixture was diluted with sat. $Na_2S_2O_3$ (2 mL) and sat. $NaHCO_3$ (2 mL) and the aqueous layer was extracted with ether (3×5 mL). Drying over $MgSO_4$, concentration, and flash chromatography (silica gel, 1.5 g, hexane:EtOAc, 8:1) afforded **15** (8.3 mg, 18.4 μmol, 90%) as a colorless oil; $[\alpha]_D^{23}$=+103 (*c* 0.06, $CHCl_3$); ν_{max} (cm^{-1}) (neat) 2929, 1776, 1731, 1457, 1376, 1317, 1191, 1128, 1079, 1039, 968, 935, 852, 727; δ_H (300 MHz, $CDCl_3$) 5.28 (1H, dd, *J*=4.1, 5.8 Hz), 5.14 (1H, s), 4.46 (1H, br s), 3.43 (3H, s), 3.08 (1H, d, *J*=4.7 Hz), 2.88 (1H, d, *J*=4.7 Hz), 2.36 (1H, br s), 2.34 (1H, dd, *J*=4.1, 14.7 Hz), 2.25 (1H, dd, *J*=5.8, 14.7 Hz), 2.04 (1H, brd, *J*=12.6 Hz), 1.94 (1H, brd, *J*=5.2 Hz), 1.89 (1H, m), 1.57–1.21 (10H, m), 1.07–0.88 (16H, m), 0.70–0.64 (4H, m); EI-MS-LR m/z (Int. %) 421 (7), 409 (M^+-iPr, 17), 377 (43), 355 (66), 281 (42); EI-MS-HR, calcd for $C_{22}H_{37}O_5Si$ (M^+-iPr): 409.2410, found: 409.2406.

5.1.7. (1*R*,2*S*,4*S*,6*R*,8*S*,10*R*)-10-Bromo-2-(diethyliso-propylsilyloxy)-4-methoxy-9-(1-methylcyclohexyl)-5,7-dioxatricyclo[6.2.1.0^{2,6}]undecane-10-carbaldehyde (17). To a solution of **15** (43.5 mg, 96.1 μmol) in CH_2Cl_2 (1.5 mL) was added dropwise $BF_3{\cdot}OEt_2$ (61 μL, 0.481 mmol) at −55°C. After stirring for 7 h, the mixture was diluted with sat. $NaHCO_3$ (2 mL), and the aqueous layer was extracted with Et_2O (4×2 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was subjected to flash chromatography (silica gel, 5.0 g, hexane:EtOAc, 10:1 to 6:1) to afford a diastereomixture (α:β=3.1:1) of **16** (34.1 mg, 75.0 μmol, 78%) as a colorless oil.

To a mixture of **16** (19.1 mg, 42.2 μmol) and HMPA (51.4 μl, 0.295 mmol) in THF (0.5 mL) was added dropwise a solution of KHMDS (0.5 M in PhMe, 0.26 mL, 0.128 mmol) at −60°C. After stirring for 20 min, a solution of NBS (51.2 mg, 0.288 mmol) in THF (0.8 mL) was added and stirring was continued at the same temperature for 2 h. The reaction was diluted with sat. NH_4Cl (2 mL) and sat. $Na_2S_2O_3$ (2 mL), and the aqueous layer was extracted with Et_2O (4×5 mL). Drying over $MgSO_4$, concentration, and flash chromatography (silica gel, 3.0 g, hexane:EtOAc, 8:1) afforded **17** (15.8 mg, 30.0 μmol, 71%) as a colorless oil; $[\alpha]_D^{23}$=−8.05 (*c* 0.174, $CHCl_3$); ν_{max} (cm^{-1}) (neat) 2935, 2875, 1722, 1455, 1376, 1189, 1126, 1037, 725; δ_H (300 MHz, $CDCl_3$) 9.55 (1H, s), 5.24 (1H, t, *J*=4.8 Hz), 4.96 (1H, s), 4.45 (1H, br s), 3.41 (3H, s), 3.25 (1H, br s), 2.96 (1H, br s), 2.33 (1H, brd, *J*=4.7 Hz), 2.23 (2H, br s), 1.56–1.19 (11H, m), 1.05–0.94 (16H, m), 0.73–0.66 (4H, m); EI-MS-LR *m/z* (Int. %) 501 (M^+−Et, 7), 487 (M^+-iPr, 8), 457 (100), 409 (64), 393 (63); EI-MS-HR, calcd for $C_{22}H_{36}O_5SiBr$ (M^+-iPr): 487.1515, found: 487.1514.

5.1.8. (1*R*,2*S*,4*S*,6*R*,8*S*,10*R*)-2-(Diethylisopropylsilyloxy)-4-methoxy-9-(1-methylcyclohexyl)-5,7-dioxatricyclo[6.2.1.0^{2,6}]undec-9-ene-10-carbaldehyde (18). To a solution of **17** (24.6 mg, 46.3 μmol) in DMF (1.0 mL) were added LiBr (42.7 mg, 0.492 mmol) and Li_2CO_3 (35.2 mg, 0.476 mmol) at 23°C, and the mixture was stirred at 125°C for 13 h. The mixture was diluted with brine (2.0 mL), and the aqueous layer was extracted with Et_2O (4×2 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was subjected to flash chromatography (silica gel, 1.2 g, hexane:EtOAc, 8:1) to afford **18** (20.2 mg, 44.9 μmol, 97%) as a pale yellow oil; $[\alpha]_D^{23}$=+97.1 (*c* 0.63, $CHCl_3$); ν_{max} (cm^{-1}) (neat) 2931, 2865, 1670, 1454, 1187, 1130, 1076, 1029, 723;δ_H (300 MHz, $CDCl_3$) 10.36 (1H, s), 5.31 (1H, dd, *J*=3.3, 6.3 Hz), 4.94 (1H, s), 4.87 (1H, br s), 3.59 (1H, d, *J*=5.2 Hz), 3.45 (3H, s), 2.40 (1H, dd, *J*=6.3, 15.1 Hz), 2.30 (1H, dd, *J*=3.3, 15.1 Hz), 2.09 (1H, d, *J*=11.8 Hz), 1.94–1.87 (2H, m), 1.77 (1H, ddd, *J*=3.0, 5.2, 11.8 Hz), 1.66–1.23 (8H, m), 1.30 (3H, s), 1.03–0.84 (13H, m), 0.67–0.57 (4H, m); EI-MS-LR *m*/*z* (Int.%) 450 (M^+, 1.0), 421 (M^+−Et, 80), 407 (M^+−*i*Pr, 17), 375 (55); EI-MS-HR, calcd for $C_{25}H_{42}O_5Si$ (M^+): 450.2801, found: 450.2813.

5.1.9. {(1*R*,2*S*,4*S*,6*R*,8*S*,10*R*)-2-(Diethylisopropylsilyloxy)-4-methoxy-9-(1-methylcyclohexyl)-5,7-dioxa-tricyclo[6.2.1.0^{2,6}]undec-9-en-10-yl}-methanol (19). To a solution of **18** (11.6 mg, 25.7 μmol) in MeOH (1 mL) were added $CeCl_3{\cdot}7H_2O$ (55 mg, 0.148 mmol) and $NaBH_4$ (5.6 mg, 0.148 mmol) at 0°C. After stirring at 0°C for 1 h, the mixture was diluted with sat. $NaHCO_3$ (1 mL) and brine (1 mL). The aqueous layer was extracted with ether (3×2 mL), dried over $MgSO_4$, and concentrated. The residue was subjected to flash chromatography (silica gel, 1.5 g, hexane:EtOAc, 8:1) to furnish **19** (9.0 mg, 20.0 μmol, 78%) as a pale yellow oil; $[\alpha]_D^{25}$=+55.1 (*c* 0.45, $CHCl_3$); ν_{max} (cm^{-1}) (neat) 3486, 2929, 2865, 1457, 1191, 1126, 1072, 1024, 979, 723; δ_H (C_6D_6, 300 MHz) 5.27 (1H, s), 5.23 (1H, dd, *J*=2.5, 6.3 Hz), 4.64 (1H, br s), 4.59 (1H, d, *J*=14.3 Hz), 4.37 (1H, d, *J*=14.3 Hz), 3.36 (3H, s), 3.19 (1H, d, *J*=4.9 Hz), 2.30 (1H, dd, *J*=2.2, 15.4 Hz), 2.18 (1H, dd, *J*=6.3, 15.4 Hz), 2.17 (1H, d, *J*=11.5 Hz), 1.84–1.64 (2H, m), 1.60 (1H, ddd, *J*=3.3, 4.9, 11.5 Hz), 1.37–1.13 (8H, m), 1.10 (3H, s), 1.05–0.83 (13H, m), 0.79–0.57 (4H, m); EI-MS-LR *m*/*z* (Int.%) 452 (M^+, 6.9), 421 (M^+−OMe, 25), 377 (100), 359 (50), 346 (64); EI-MS-HR, calcd for $C_{25}H_{44}O_5Si$ (M^+): 452.2958, found: 452.2936.

5.1.10. {(1*S*,3*R*,5*S*,7*S*,8*R*,9*R*,11*R*)-7-(Diethylisopropylsilyloxy)-5-methoxy-11-(1-methylcyclohexyl)-2,4,10-trioxa-tetracyclo[6.3.1.0^{3,7}0^{9,11}]dodec-9-yl}-methanol (20). To a solution of **19** (5.7 mg, 12.6 μmol) in CH_2Cl_2 (1.0 mL) were added $VO(acac)_2$ (1.0 mg, 3.77 mmol) and a solution of TBHP (3.05 M in CH_2Cl_2, 43 μl, 131 μmol) at 0°C, and the mixture was stirred at 23°C for 3.5 h. The mixture was diluted with sat. $Na_2S_2O_3$ (2 mL), and the aqueous layer was extracted with Et_2O (3×2 mL). Drying over $MgSO_4$, concentration, and flash chromatography (silica gel, 1.2 g, hexane:EtOAc, 8:1) afforded **20** (12.6 μmol, 100%) as a colorless oil; $[\alpha]_D^{24}$=+22.4 (*c* 0.25, $CHCl_3$); ν_{max} (cm^{-1}) (neat) 3494, 2935, 2867, 1457, 1373, 1317, 1241, 1195, 1126, 1083, 1033, 958, 887, 765, 723; δ_H (300 MHz, $CDCl_3$) 5.33 (1H, s), 5.27 (1H, dd, *J*=3.0, 6.3 Hz), 4.56 (1H, br s), 4.31 (1H, dd, *J*=7.4, 12.4 Hz), 4.02 (1H, dd, *J*=6.0, 12.4 Hz), 3.41 (3H, s), 2.90 (1H, d, *J*=5.2 Hz), 2.58 (1H, m), 2.44 (1H, dd, *J*=6.3, 15.4 Hz), 2.36 (1H, dd, *J*=3.0, 15.4 Hz), 1.73–1.43 (12H, m),1.23 (3H, s), 1.06–0.88 (13H, m), 0.79–0.69 (4H, m); δ_C (75 MHz, $CDCl_3$) 129.0, 108.0, 106.7, 68.0, 62.3, 62.1, 46.4, 45.3, 29.7, 26.4, 25.9, 22.0, 17.6, 17.5, 17.3, 14.1, 7.3, 7.1, 4.8, 4.7; EI-MS-LR *m*/*z* (Int.%) 468 (M^+, 1.9), 425 (M^+−*i*Pr, 10), 393 (39), 244 (78); EI-MS-HR, calcd for $C_{25}H_{44}O_6Si$ (M^+): 468.2907, found: 468.2916.

5.1.11. (1*S*,3*R*,5*S*,7*S*,8*R*,9*R*,11*R*)-7-(Diethylisopropylsilyloxy)-9-iodomethyl-5-methoxy-11-(1-methylcyclohexyl)-2,4,10-trioxatetracyclo[6.3.1.0^{3,7}0^{9,11}]dodecane (21). To a solution of alcohol **20** (6.2 mg, 13.2 μmol) in THF (0.5 mL) were added imidazole (28.0 mg, 0.411 mmol), PPh_3 (53.0 mg, 0.202 mmol) and a solution of I_2 (51.0 mg, 201 μmol) in THF (0.5 mL). After stirring at 23°C for 8 h, the reaction was diluted with sat. $NaHCO_3$ (1 mL) at 0°C. To the mixture was added a solution of I_2 in THF until the solution persisted in yellow–brown color. After addition of sat. $Na_2S_2O_3$ (20 mL) at 0°C, the aqueous layer was extracted with ether (4×2 mL), dried over $MgSO_4$, and concentrated. The residue was subjected to flash chromatography (silica gel, 1.5 g, hexane:EtOAc, 10:1) to furnish iodide **21** (6.2 mg, 10.8 μmol, 82%) as white solids; $[\alpha]_D^{23}$=+12.5 (*c* 0.30, $CHCl_3$); ν_{max} (cm^{-1}) (neat) 2929, 2863, 1457, 1373, 1315, 1247, 1195, 1124, 1085, 883, 767, 723; δ_H (300 MHz, $CDCl_3$) 5.28 (1H, s), 5.25 (1H, dd, *J*=2.7, 6.3 Hz), 4.63 (1H, br s), 4.43 (1H, d, *J*=9.6 Hz), 3.77 (1H, d, *J*=9.6 Hz), 3.40 (3H, s), 2.90 (1H, brd, *J*=5.2 Hz), 2.42 (1H, dd, *J*=6.3, 15.7 Hz), 2.32 (1H, dd, *J*=2.7, 15.7 Hz), 1.77–1.34 (12H, m), 1.25 (3H, s), 1.06–0.83 (13H, m), 0.80–0.64 (4H, m); EI-MS-LR *m*/*z* (Int. %) 547 (M^+−OMe, 8.7), 534 (21), 451 (100); EI-MS-HR, calcd for $C_{24}H_{40}O_4SiI$ (M^+−OMe): 547.1741, found: 547.1729.

5.1.12. (1*S*,3*R*,5*S*,7*S*,8*R*,9*R*,11*R*)-7-(Diethylisopropylsilyloxy)-9-methyl-5-methoxy-11-(1-methylcyclohexyl)-2,4,10-trioxatetracyclo[6.3.1.0^{3,7}0^{9,11}]dodecane (22). To a solution of **21** (3.2 mg, 5.5 μmol) in CH_3CN (1.0 mL) was added $NaBH_4$ (6.1 mg, 0.161 mmol) at 0°C, and the mixture was refluxed for 18 h. The reaction was diluted with brine (2 mL), and the aqueous layer was extracted with Et_2O (3×2 mL). Drying over $MgSO_4$, concentration, and flash chromatography (silica gel, 1.5 g, hexane:EtOAc, 10:1) furnished **22** (2.2 mg, 4.9 μmol, 88%) as a colorless oil; $[\alpha]_D^{26}$=+17.3 (*c* 0.11, $CHCl_3$); ν_{max} (cm^{-1}) (neat) 2927, 2865, 1457, 1371, 1267, 1193, 1126, 1079, 1033, 964, 723; δ_H (300 MHz, $CDCl_3$) 5.29 (1H, s), 5.26 (1H, dd, *J*=3.6, 5.8 Hz), 4.52 (1H, br s), 3.41 (3H, s), 2.43 (1H, brd, *J*=4.7 Hz), 2.34 (1H, brd, *J*=5.8 Hz), 2.33 (1H, brd, *J*=3.6 Hz), 1.77 (3H, s), 1.70–1.43 (12H, m), 1.23 (3H, s), 1.03–0.95 (13H, m), 0.74–0.68 (4H, m); EI-MS-LR *m*/*z* (Int.%) 452 (M^+, 2.5), 421 (M^+−OMe, 2.0), 409 (M^+−*i*Pr, 3.4), 377 (4.6), 263 (100); EI-MS-HR, calcd for $C_{25}H_{44}O_5Si$ (M^+): 452.2958, found: 452.2966.

5.1.13. (1*S*,3*S*,7*S*,8*S*,9S,11*S*)-7-Hydroxy-9-methyl-11-(1-methylcyclohexyl)-2,4,10-trioxatetracyclo[6.3.1.0^{3,7}0^{9,11}]dodec-5-ene (23). To a mixture of **22** (6.5 mg, 14.4 μmol) and MS4A (ca. 20 mg) in CH_3CN (1 mL) was added dropwise PhSeH (30.5 μl, 287 μmol) at 23°C.

Amberlyst 15 was added and the mixture was stirred at 23°C for 30 min. After filtration through Celite and $NaHCO_3$, the filtrate and washings were concentrated in vacuo to afford a crude selenide. The crude selenide was used for next reaction without further purification.

To a solution of crude selenyl compound in CH_2Cl_2 (1.0 mL) were added dropwise 35% H_2O_2 (5 drops) and pyridine (5 drops) at 0°C, and the mixture was stirred for 30 min. To the solution was added dropwise sat. $Na_2S_2O_3$ (2 mL), and the aqueous layer was extracted with Et_2O (2×3 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was subjected to flash chromatography (silica gel, 1.2 g, hexane:EtOAc, 10:1 to 5:1) to afford a crude dihydrofuran (1.6 mg), along with recovered **22** (1.4 mg, 3.1 μmol) in 22% yield.

To a solution of the dihydrofuran (1.6 mg) in THF (1 mL) was added dropwise a solution of TBAF (1.0 M in THF, 11.4 μl, 11.4 μmol) at 0°C. After stirring for 10 min, the mixture was diluted with sat. NH_4Cl (2.0 mL), and the aqueous layer was extracted with Et_2O (2×3 mL). The residue was subjected to flash chromatography (silica gel, 1.5 g, hexane:EtOAc, 10:1 to 4:1) to furnish **23** (0.8 mg, 2.7 μmol, 19% for 3 steps) as white solids; $[\alpha]_D^{25}=-112$ (*c* 0.04, $CHCl_3$); ν_{max} (cm^{-1}) (neat) 3442, 2925, 2856, 1698, 1617, 1523, 1459, 1018, 773; δ_H (300 MHz, $CDCl_3$) 6.49 (1H, d, *J*=2.7 Hz), 5.51 (1H, s), 5.15 (1H, d, *J*=2.7 Hz), 4.48 (1H, d, *J*=3.6 Hz), 2.39 (1H, d, *J*=5.8 Hz), 1.82 (3H, s), 1.76–1.15 (12H, m), 1.27 (3H, s); δ_C (125 MHz, $CDCl_3$) 147.9, 108.3, 107.5, 83.4, 76.4, 75.9, 65.7, 46.5, 35.3, 27.3, 26.0, 22.4, 22.0, 17.4, 14.1; EI-MS-LR *m/z* (Int. %) 292 (M^+, 0.9), 192 (100); EI-MS-HR, calcd for $C_{17}H_{24}O_4$ (M^+): 292.1675, found: 292.1674.

Acknowledgements

This work was financially supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan (13680665 and 14044001) and The Akiyama Foundation.

References

1. (a) Murai, A. In *Pesticide Science and Biotechnology*; Greenhalgh, R., Roberts, T. R., Eds.; Blackwell: London, 1987; pp 81–88. (b) *Neem: A Tree for solving Global Problems*; National Research Council, National Academy: Washington, DC, 1992. (c) Gill, J. S.; Lewis, C. T. *Nature* **1971**, *232*, 402. (d) Ruscoe, C. N. E. *Nature* **1972**, *236*, 159. (e) Rembold, H.; Garcia, D. W. E. *J. Insect. Physiol.* **1984**, *30*, 939. (f) Redfern, R. E.; Hayes, D. K.; Warthen, J. D.; DeMilo, A. B.; McGovern, T. P. *Ann. Rev. Chronopharmacol.* **1984**, *1*, 239. (g) Koul, O. *Entomol. Exp. Appl.* **1984**, *36*, 85. (h) Mordue (Luntz), A. J.; Blackwell, A. *J. Insect Physiol.* **1993**, *39*, 903. (i) Govindachari, T. R.; Gopalakrishnan, G. *J. Indian Chem. Soc.* **1998**, *75*, 655.
2. (a) Butterworth, J. H.; Morgan, E. D. *Chem. Commun.* **1968**, 23. (b) Butterworth, J. H.; Morgan, E. D. *J. Insect Physiol.* **1971**, *17*, 969. (c) Butterworth, J. H.; Morgan, E. D.; Percy, G. R. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2445. (d) Morgan, E. D.; Butterworth, J. H. *Phytochemistry* **1973**, *12*, 391.
3. (a) Kraus, W.; Bokel, M.; Klenk, A.; Pöhnl, H. *Tetrahedron Lett.* **1985**, *26*, 6435. (b) Broughton, H. B.; Ley, S. V.; Slawin, A. M. Z.; Williams, D. J.; Morgan, E. D. *J. Chem. Soc., Chem. Commun.* **1986**, 46. (c) Turner, C. J.; Tempesta, M. S.; Taylor, R. B.; Zagorski, M. G.; Termini, J. S.; Schroeder, D. R.; Nakanishi, K. *Tetrahedron* **1987**, *43*, 2789.
4. Ley, S. V.; Lovell, H.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1992**, 1304.
5. (a) Ley, S. V.; Denholm, A. A.; Wood, A. *Nat. Prod. Rep.* **1993**, 109. and references cited therein. (b) Nishikimi, Y.; Iimori, T.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1989**, *54*, 3354. (c) Henry, K. J., Jr.; Fraser-Reid, B. *J. Org. Chem.* **1994**, *59*, 5128. (d) Watanabe, H.; Watanabe, T.; Mori, K. *Tetrahedron* **1996**, *52*, 13939. (e) Watanabe, H.; Watanabe, T.; Mori, K.; Kitahara, K. *Tetrahedron Lett.* **1997**, *38*, 4429. (f) Scheliger, H.; Winterfeldt, E. *Chirality* **1997**, *9*, 454. (g) Haag, D.; Chen, X.-T.; Fraser-Reid, B. *Chem. Commun.* **1998**, 2577. (h) Ley, S. V.; Gutteridge, C. E.; Pape, A. R.; Spilling, C. D.; Zumbrunn, C. *Synlett* **1999**, 1295. (i) Nicolaou, K. C.; Follmann, M.; Roecker, A. J.; Hunt, K. W. *Angew. Chem. Int. Ed.* **2002**, *41*, 2103. (j) Nicolaou, K. C.; Roecker, A. J.; Follmann, M.; Baati, R. *Angew. Chem. Int. Ed.* **2002**, *41*, 2107. (k) Durand-Reville, T.; Gobbi, L. B.; Gray, B. L.; Ley, S. V.; Scott, J. S. *Org. Lett.* **2002**, *4*, 3847. (l) Nicolaou, K. C.; Roecker, A. J.; Monenschein, H.; Guntupalli, P.; Follmann, M. *Angew. Chem. Int. Ed.* **2003**, *42*, 3637.
6. (a) Simmonds, M. S.; Blaney, W. M.; Grossman, R. B.; Ley, S. V. *J. Insect Physiol.* **1995**, *41*, 555. (b) Nisbet, A. J.; Mordue (Luntz), A. J.; Grossman, R. G.; Jennens, L.; Ley, S. V.; Mordue, W. *Arch. Insect Biochem. Physiol.* **2001**, *46*, 78.
7. Yamasaki, B.; Kloche, J. A. *J. Agric. Food Chem.* **1987**, *35*, 467.
8. Ley, S. V.; Anderson, J. C.; Blaney, W. M.; Jones, P. S.; Lidert, Z.; Morgan, E. D.; Robinson, N. G.; Santafianos, D.; Simmonds, M. S. J.; Toogood, P. L. *Tetrahedron* **1989**, *45*, 5175.
9. Ley, V. S.; Santafianos, D.; Blaney, W. M.; Simmonds, M. S. J. *Tetrahedron Lett.* **1987**, *28*, 221.
10. (a) Baldoni, H. A.; Enriz, R. D.; Jáuregui, E. A.; Csizmadia, I. G. *J. Mol. Struct. (Theochem)* **1996**, *363*, 167. (b) Baldoni, H. A.; Enriz, R. D.; Csizmadia, I. G. *J. Mol. Struct. (Theochem)* **1999**, *463*, 251. (c) Enriz, R. D.; Baldoni, H. A.; Zamora, M. A.; Jáuregui, E. A.; Sosa, M. E.; Tonn, C. E.; Luco, J. M.; Gordaliza, M. *J. Agric. Food Chem.* **2000**, *48*, 1384.
11. (a) Kanoh, N.; Ishihara, J.; Murai, A. *Synlett* **1995**, 895. (b) Kanoh, N.; Ishihara, J.; Murai, A. *Synlett* **1997**, 737. (c) Ishihara, J.; Fukuzaki, T.; Murai, A. *Tetrahedron Lett.* **1999**, *40*, 1907. (d) Ishihara, J.; Yamamoto, Y.; Kanoh, N.; Murai, A. *Tetrahedron Lett.* **1999**, *40*, 4387. (e) Kanoh, N.; Ishihara, J.; Yamamoto, Y.; Murai, A. *Synthesis* **2000**, 1878. (f) Yamamoto, Y.; Ishihara, J.; Kanoh, N.; Murai, A. *Synthesis* **2000**, 1894.
12. Fukuzaki, T.; Kobayashi, S.; Hibi, T.; Ikuma, Y.; Ishihara, J.; Kanoh, N.; Murai, A. *Org. Lett.* **2002**, *4*, 2877.
13. (a) Ishizumi, K.; Koga, K.; Yamada, S. *Chem. Pharm. Bull.* **1968**, *16*, 492. (b) Itaya, T.; Fujii, T.; Evidente, A.; Randazzo, G.; Surico, G.; Iacobellis, N. *Tetrahedron Lett.* **1986**, *27*, 6349.
14. (a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin*

Trans. I **1975**, 1574. (b) Barton, D. H. R.; Motherwell, W. B.; Stange, A. *Synthesis* **1981**, 743.
15. Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *Tetrahedron* **1993**, *49*, 7193.
16. (a) Ireland, R. E.; Muchmore, D. C.; Hengartner, U. *J. Am. Chem. Soc.* **1972**, *94*, 5098. (b) Rigby, J. H. *Tetrahedron Lett.* **1982**, *23*, 1863. (c) Trost, B. M.; Renaut, P. *J. Am. Chem. Soc.* **1982**, *104*, 6668. (d) Wender, P. A.; von Geldern, T. W.; Levine, B. H. *J. Am. Chem. Soc.* **1988**, *110*, 4858. (e) Boukouvalas, J.; Cheng, Y.-X.; Robichaud, J. *J. Org. Chem.* **1998**, *63*, 228.
17. Liu, H.-J.; Shang, S. *Tetrahedron Lett.* **1998**, *39*, 367.
18. (a) Hutchins, B. O.; Maryanoff, B. E.; Milewski, C. A. *J. Chem. Soc., Chem. Commun.* **1971**, 1097. (b) Hutchins, B. O.; Kandasamy, D.; Maryanoff, C. A.; Masilamani, C. D.; Maryanoff, B. E. *J. Org. Chem.* **1977**, *42*, 82.
19. Hutchins, B. O.; Kandasamy, D.; Dux, F.; Maryanoff, C. A.; Rotstein, D.; Goldsmith, B.; Burgoyne, W.; Cistone, F.; Dalessandro, J.; Puglis, J. *J. Org. Chem.* **1978**, *43*, 2259.
20. (a) Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1973**, *38*, 3224. (b) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 3775.
21. (a) Crabtree, R. H.; Felkin, H.; Morris, E. E. *J. Organometal. Chem.* **1977**, *141*, 205. (b) Baudry, D.; Ephritikhine, M.; Felkin, H. *J. Chem. Soc., J. Chem. Commun.* **1978**, 694.
22. (a) Breslow, R.; Baldwin, S. W. *J. Am. Chem. Soc.* **1970**, *92*, 732. (b) Baldwin, J. E.; Bhatnagar, A. K.; Harper, R. W. *J. Chem. Soc., J. Chem. Commun.* **1970**, 659.
23. Deleris, G.; Dunogues, J.; Gadras, A. *Tetrahedron* **1988**, *44*, 4243.
24. The stereochemstry of **15** was determined by its NOE correlation.
25. Noller, H.; Andréu, P.; Hunger, M. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 172.
26. Luche, J.-L.; Gemal, A. L. *J. Am. Chem. Soc.* **1979**, *101*, 5848.
27. Anderson, J. C.; Ley, S. V.; Santafianos, D.; Sheppard, R. N. *Tetrahedron* **1991**, *47*, 6813.